**Template guidelines:** For your grant application, the SERCC strongly recommends using the words that are underlined below including the highlighting (i.e., italics, underlining, bolding). The remaining text in bullet points is provided as a suggestion.

**Specific Aims**

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| Opening sentence: *A sentence to immediately capture the reviewers’ attention and highlight an area relevant to the targeted program/funding agency.*WhyCurrent knowledge: *Information about what is known that will allow reviewers to understand the importance of the proposed research. Sets up the gap/unmet need.*Knowledge gap or statement of need: *The subject of the proposal; must relate to the previous statements as a next step to advance the field. (Note: It is not essential to use the term “knowledge gap” in this sentence.)*Consequence(s) of not addressing knowledge gap or need: *Explain why failing to address this gap/need will prevent vertical advancement of the field.* |

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| Long-term goal: *The goal of your research over multiple funding periods. This must be broader than “overall objective.”** “Our *long-term goal* is to…”

Overall objective: *What will be accomplished through this project; must link back to the gap/need you are addressing.*What* “The *overall objective* of the proposed research is to…”

Central hypothesis: *What must be tested to attain the objective. This should be broad; details will be provided in specific aims.** “Our *central hypothesis* is that…”

Data to support hypothesis: *Your preliminary data (just the punchline), and work by others if relevant.*Rationale: *What attaining your objective will allow you to do and how that will advance the field (vertically); must link back to knowledge gap/statement of need.* **[Include only if it is not repetitive of information in the "Why" paragraph.]** *For some mechanisms, it can be useful to instead briefly describe expertise or resources that make you/your team well suited to perform the proposed studies.* |

Specific Aims: *The aims paragraphs should each contain minimally a title and a working hypothesis. These should make it clear which component of the central hypothesis is tested in that aim—and why. Each title should be broad and open-ended; the working hypothesis can provide the focus of the aim. If you have no room to expand on how you will achieve your aim in an additional sentence or two, be sure that your working hypothesis gives a sense of approach and experimental readout.*

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| **Aim 1: Title**Working hypothesis: | **Aim 2: Title**Working hypothesis: | **Aim 3: Title**Working hypothesis: |

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| Expected outcomes & broader impact: *What your aims are likely to produce, how that would contribute to the overall objective, and what broader impact this would have on this area of research.*Payoff* “The *expected outcomes* are …”

Broader impact* “The *broader impact* is…”
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**Research Strategy**

**Significance** (subsection): *(1–1.5 pages) Place the proposed work within the context of the overall mission of the funding agency, justify the need for what you propose, explain previous findings on which you base your studies (including their rigor), and indicate the positive effect that completing the project will have on the problem you are addressing.*

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| **Importance of the problem:** *(1 paragraph, ~0.25 pages) An extension of the information provided in first paragraph of the Specific Aims page, e.g., what problem or critical barrier your research addresses (substantiated with documentation from the literature) and the negative consequences of not meeting the need. Be sure to go from* ***broad to specific****; do not interrupt the flow with a statement of what you plan/expect to accomplish—save this for the* ***Significance of the expected research contribution*** *subsection below.*

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| *Suggested paragraph order and phrasing* | *Statement describing the key underlying problem being addressed* |
| *“It is widely appreciated that…”* |
| *“There is a clear lack of…”* |
| *“Thus, there is an urgent need…”* |

**Scientific premise and rigor of prior research** (previously, scientific premise): *(several paragraphs, ~0.5–0.75 pages) The foundation on which your proposal is built and your evaluation of how reliable it is.* ***Organize by aim or overall.*** *Discuss: the strengths and weaknesses in the rigor of prior research (both published studies and unpublished preliminary data) that serves as the key support for the proposed project. Note that it may be more appropriate to discuss limitations rather than issues with rigor. End this by including general statements (leave details for Approach section) about how weaknesses of prior research will be overcome. Cite only the strongest supporting publications.*

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| *Suggested paragraph order and phrasing* | *“Numerous studies have…”* |
| *“However, studies X and Y have important limitations in that…”* |
| *“In addition, the rigor of study Z is not sufficient in that the antibody…”* |
| *“To overcome these gaps in rigor, we will…” [keep this general]* |
| *“Thus, our proposed studies will circumvent the limitations of…by…”* |

**Significance of the expected research contribution**: *(1 paragraph, ~0.25 pages) The research contributions you expect to make; these should be relevant to the mission of the funding agency. Write about contributions to science in general vs. your field separately as suggested below, or in a single paragraph. In each paragraph your argument should go from* ***specific to broad****.** Impact of the project on the field: *How the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field will be advanced (vertically) if the proposed aims are achieved.*
* Impact of the project on scientific knowledge: *How the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more fields.*
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**Innovation** (subsection): *(*≤*0.5 pages)* *Explain what makes your proposed approach a new and substantially different way of addressing an important problem.*

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| * Strategies currently used to address the problem of interest and their limitations: *Why they are unsatisfactory.*
* What makes the proposed research innovative: *How the proposed project differs from the status quo. This can include a new approach or the use of an unconventional technology, but should open new horizons.*
* Advancements that are only possible because of this new approach.

Alternative: Provide a bulleted list of points that highlight what makes your proposal innovative. *For each include: what was done previously and why that was unsatisfactory; what new approaches or new technologies are being employed; and how the new approaches overcome previous limitations.* |

**Research Strategy (con’t)**

**Approach** (subsection):

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| **Progress report:** *(0.25 pages)* **For Renewal Applications only.** **Consider presenting this information in table format (see example on page 8).*** *List the beginning and ending dates for the period covered since the last competitive review, as well as the aims (can be paraphrased) for the previous funding period.*
* *Provide a summary of progress toward meeting objectives during that period, the importance of the findings, publications, and any significant changes/new directions, including any resulting from significant budget reductions.*
* *For any studies meeting the NIH definition for clinical research, include previous participant enrollment (e.g., recruitment, retention, inclusion of women, minorities, children, etc.).*
* *Only refer to publications, patents, or printed materials generated during the previous award period, e.g., “We published a study showing xxx (Science*, 2023).” *Provide the full citation in the "Progress Report Publication List" attachment.*
* ***Do not*** *list full citations for publications, patents, other printed materials.*
* ***Do not*** *use the Progress Report to duplicate information collected elsewhere in the application (discuss only).*

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| *Suggested paragraph order and phrasing* | *“During the past funding cycle (x/x/xx–xx/xx/xx), our objectives were to …”* |
| *“Our productivity is illustrated by…” [follow with description of work in table or paragraph format; example of table format on page 8]* |

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| **Issues related to rigor and reproducibility:** *For paragraphs on* ***Addressing weaknesses in rigor of prior research,******Strategies to ensure rigor of the proposed research*** *and* ***Considerations of biological variables including sex****, authors should provide relevant information that clearly addresses all points. This can be done:** *at the beginning or end of the Approach subsection (advisable if applicable to all aims), or*
* *in each aim (if information differs by aim).*

*The key is to make all information on the topic of R&R easy to find, i.e.* ***the paragraphs should be labeled****.*Addressing weaknesses in rigor of prior research **–** *(0.25 pages)* *Describe plans to address weaknesses in rigor of the prior research that serves as key support for the proposed project.*

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| *Suggested paragraph order and phrasing* | *“As described under Significance, the key weaknesses of past studies of xxx are yyy.”* |
| *“In the current study, we will address yyy.”* |
| *“In addition, we will ensure the proposed research is performed rigorously, as described below.”* |

Strategies to ensure rigor of the proposed research – *(0.25 pages) Describe how you will ensure a robust and unbiased approach appropriate for the work proposed. Strategies may include:* * *Randomization protocol for sample groups*
* *Blinded data recording and analysis*
* *Controls and replicates needed*
* *Sample size estimation/power analysis (critical for studies using human subjects or higher vertebrates)*
* *Principles of Good Laboratory Practice*
* *Essential reagents and their authentication*
* *Statistical analyses to be used*

[Adapted from Landis SC et al. (2012). *Nature* Oct. 11; 490(7419):181-91.](https://www.ncbi.nlm.nih.gov/pubmed?term=nature%5BJour%5D+AND+2012%5Bpdat%5D+AND+landis%5Bauthor%5D&cmd=detailssearch)Consideration of biological variables, including sex, in the proposed research – *(0.25 pages) Include:** *Sex (required; e.g. inclusion of equal numbers of each; impact on results; separate analysis of results; karyotype of cell lines)*
* *Weight, age, and health status, if applicable*
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**Research Strategy (con’t) OPTION A**

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| **Aim** **1:** *Title to be repeated verbatim from Specific Aims page.* Rationale: *Remind the reader of the specific problem/question being addressed in this aim. Provide evidence for your hypothesis (i.e. premise) in the form of preliminary data/data from the literature. End with a paragraph stating the working hypothesis, a brief description of the approach to be used to address this, and the significance of accomplishing this aim.* Experimental Design: *For each activity posed, provide an informative title that relays the goal/question being addressed. In the paragraph, include a sentence or two to relay the justification for what needs to be learned/rationale for the experiment, the general experimental approach, which can include preliminary data to show feasibility, details on how the approach works, and what results are expected/what will be learned.**Subaim/Experiment 1**Subaim 2/Experiment 2**Subaim 3/Experiment 3* Expected outcomes:*Short paragraph (1/8-1/4 of a page) that integrates outcomes from all proposed activities within this aim, and indicates how they will contribute to achieving the overall objective.*Potential problems and alternative strategies:*Essential for each aim. Propose alternatives in case your hypothesis is proven invalid/critical reagents fail/approaches are inconclusive. These problems should not be fatal to your proposal; even if they occur, the alternatives described here should enable you to achieve the main objectives. Be sure to phrase as conditional statements (e.g., if xxx were to happen, we would do yyy).* |

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| **Aim 2:** (as above) |

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| **Aim 3:** (as above) |

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| **Timeline and benchmarks for success:** *Preferred in table format. Demonstrate that you have thoroughly considered how long it will take to complete each component proposed. Include when you expect to achieve certain benchmarks (be sure to specify what these are).* |

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| **Future directions:** *Brief summary of where you expect the science to be at the conclusion of the proposed research. Include the next expected steps and why they are important.* |

**Research Strategy (con’t) – OPtion B**

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| **Prior/Preliminary Data:** *These should be key pieces of information that provide the premise or support the feasibility of the aim. Include a section for each major point that is made, presenting the data in a way that tells a story and leads up to the knowledge gap. For each major point, be sure to include an informative subheading and describe:** *The question that was asked*
* *What was done to answer the question*
* *The methods used*
* *The results*
* *If the work was done rigorously (particularly relevant for published data)*
* *What the results mean in the context of this proposal*

**Overall Study Design:**Justification for study design: *Describe the approach you will be taking, include justification for your approach (with preliminary data if relevant), and describe how this approach and activities described below will allow you to test the central hypothesis or accomplish the aims.*Sections for each major element/activity relevant to the whole study**:** *These could be about sample populations, experimental methods, techniques, procedures, biomarkers assessed, study team, etc. Be sure to first state why a particular task needs to be done, e.g., why a specific population needs to be recruited. Then describe the approach that you will use; figures/graphics are ok to include to relay this information.* Statistical analysis:*Discuss here only if relevant to the overall study design or common across the whole study. Otherwise, discuss within each aim.* Potential problems and alternative approaches: *Discuss only issues that are relevant to the Overall Study Design, e.g., participant retention, issues with data or sample gathering.***Aim** **1:** *Title to be repeated verbatim from Specific Aims page.* Rationale: *Limit to 4-6 sentences; remind the reader of the problem/question being addressed, the working hypothesis (if relevant), the approach that you will use, and the results expected and how they will move the project forward.* Experimental Design: *For each activity posed, provide an informative title that relays the goal/question being addressed. In the paragraph, include a sentence or two to relay the justification for what needs to be learned or rationale for the experiment, the general experimental approach (can include preliminary data to show feasibility, details on how the approach works, and what results are expected/what will be learned).**Subaim/Experiment 1**Subaim 2/Experiment 2**Subaim 3/Experiment 3* Expected outcomes:*Short paragraph (1/8-1/4 of a page) that integrates outcomes from all proposed activities within this aim, and indicates how they will contribute to achieving the overall objective.*Potential problems and alternative strategies:*Essential for each aim. Propose alternatives in case your hypothesis is proven invalid/critical reagents fail/approaches are inconclusive. These problems should not be fatal to your proposal; even if they occur, the alternatives described here should enable you to achieve the main objectives. Be sure to phrase as conditional statements (e.g., if xxx were to happen, we would do yyy).* |

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| **Aim 2:** (as above) |

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| **Aim 3:** (as above) |

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| **Timeline and benchmarks for success:** *Preferred in table format. Demonstrate that you have thoroughly considered how long it will take to complete each component proposed. Include when you expect to achieve certain benchmarks (be sure to specify what these are).* |

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| **Future directions:** *Brief summary of where you expect the science to be at the conclusion of the proposed research. Include the next expected steps and why they are important.* |

**Specific Aims Page**

Multiple Sclerosis (MS) is an autoimmune disease characterized by demyelination of neurons in the central nervous system, and one of its most common clinical presentations is high levels of fatigue. This disease takes a heavy toll in that xxx. Notwithstanding its impact on society and extensive efforts to xxx, little is known about the underlying causes or how to ameliorate the symptoms and improve the quality of life for patients. Currently, one of the few available clues is a link between lipid intake by patients and a reduction in fatigue. This is based on a study in which 19 MS patients adhered to a paleolithic diet for 12 months and reported a dramatic reduction in levels of fatigue. The specific physiological reasons for the change in this set of patients on the “Wahls diet” is unknown, in large part because of the complexities of analyzing metabolic data in combination with the small size of the patient population. However, metabolomic data suggest that changes in lipid profile are associated with severity of clinical symptoms experienced by patients with MS. I contend that improvements in statistical analysis will make it possible to address the following *critical need:* to identify key changes in the metabolism that are the underpinnings of disease, in MS patients and others.

My *long-term goal* as a physician scientist is to statistically identify metabolic imbalances associated with fatigue levels observed in patients with MS. The main *objective of the proposed research* is to develop a statistical methodology that will make possible a meaningful analysis of metabolomics data, which by its nature is highly dimensional, i.e. for which the number of samples collected is smaller than the number of variables. Specifically, I propose to develop a penalized regression method with less bias than those typically in use, to provide more accurate analysis and make possible the identification of the lipids that account for the changes in patient fatigue. My *central hypothesis* is that use of penalty criterion that is adequate to xxx in the penalized regression model will make it possible to determine which specific lipid changes make the main contribution to the improved levels of fatigue seen in MS patients who participated in the Wahls diet. The *rationale* for undertaking this study is that developing a more accurate penalty criterion will improve existing penalized regression models and, when applied to this data set, make it possible to identify specific metabolic imbalances in patients with MS and tjis guide personalized treatment.

**Aim 1: Design a Penalty Criterion that is Adequate for the Penalized Regression Methods**

Current penalization criteria use a constant to constrain the value of estimates in regression models, and for highly dimensional samples this leads to strongly biased estimates. I propose to design a penalty function instead of a penalty constant, which will make it possible to assign specific penalties to each variable. I will develop the mathematical foundation of this penalty function and compare its performance on a set of 19 MS patients and 19 controls to that of current methods, using metabolic data documented in the literature.

**Aim 2: Identify Lipids Associated with Fatigue Levels in Patients with Multiple Sclerosis**

Although current penalized regression methods give biased estimates when samples are small and highly dimensional, they can nevertheless provide information about the overall importance of the variables that are being analyzed should the development of more effective methods prove a challenge. Thus, I will apply current as well as newly developed methods of penalization to the Wahls diet data set, and identify the lipids that are associated with changes in fatigue levels in these MS patients. Lipids will be identified by sequencing using mass spectrometry, followed by application of the various regression models to explain the variability of fatigue as a function of the lipid profile.

The *expected outcomes* of the proposed research are a new type of penalty criterion that will both improve the accuracy of analysis of data from small samples with high dimensionality and make it possible to identify specific metabolic imbalances in patients with MS. The *broader impact* of these discoveries will be progress in the treatment of MS, as well as in the study of complex diseases more generally. The *impact on my career goals* will be preparation for my role as a physician scientist, providing me with skills in statistical methodologies that can be applied to a broad range of conditions.

**Progress report (07/01/20xx-present).** During the previous funding period, we made major progress on the previously proposed aims as outlined below. ## publications related to, and supported by, this grant (among a total of ##) are included in the Progress Report Publication List.

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|  | **Findings** | **Publications** |
| ***Aim 1*** | *Determined that chocolate increases heterochromatin formation in B cells to induce antibody production.*  | *Nature, 2021; PNAS, 2022* |
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| ***Aim 2*** |  |  |
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| ***Aim 3*** |  |  |
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